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# Ventilator-associated pneumonia

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**Keywords:** anti-infective agents; ICU; nosocomial infection; ventilator-associated pneumonia

**Learning objectives:**
By reading this article you should be able to:

- Explain the epidemiology of ventilator-associated pneumonia (VAP) and the differences between definitions.
- Appreciate the strengths and limitations of different microbiological techniques used to support the diagnosis of VAP.
- Evaluate the evidence for different strategies for preventing VAP.
- Apply knowledge of guideline-recommended strategies in managing VAP.

Ventilator-associated pneumonia (VAP) is a common complication of invasive ventilation that afflicts critically ill patients and is associated with increased morbidity and mortality. However, it is unclear if a causal relationship exists between the development of VAP and poor outcomes. Multiple interventions have been evaluated to prevent and treat VAP. However, these have not necessarily translated to improved outcomes despite reducing the incidence of VAP. Moreover, the definition and diagnostic criteria for VAP vary, posing challenges in quantifying the global burden of VAP and its effect on patient outcomes.

**Key points**

- The incidence of ventilator-associated pneumonia varies significantly between different regions of the world.
- Many factors could explain the differences in incidence, including how VAP is defined and diagnosed.
- Several strategies have been proposed to prevent VAP, with varying degrees of effectiveness.
- Recent studies evaluating the route and optimal duration of antimicrobial therapy may improve outcomes from VAP whilst reducing the potential risks of increasing antimicrobial resistance.
- Current international guidelines vary in their recommendations for the management of VAP.

In this article we compare the contemporary definitions of VAP and describe clinical decision-making criteria for estimating its risk. We then review novel diagnostic techniques to aid early and accurate diagnosis of VAP, explaining their advantages and disadvantages. We explore risk factors for VAP, the commonly implicated organisms and the association between VAP and patient-centred outcomes.

Subsequently, we summarise the emerging evidence supporting proposed strategies to prevent VAP and describe potential pitfalls, including the challenges of researching therapies aimed at VAP prevention and patient outcomes.

Finally, we review the evidence and guideline recommendations for treating VAP, focusing on specific aspects of antimicrobial therapy.

## Pathogenesis, epidemiology and diagnosis

### Pathogenesis

The pathogenesis of VAP depends on several factors, including alterations in the airway secondary to tracheal intubation, changes in the patient's microbiological flora and

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Table 1 Comparison of the HELICS and CPIS criteria for diagnosing ventilator-associated pneumonia. CPIS, Clinical Pulmonary Infection Score; HELICS, Hospitals in Europe Link for Infection Control Through Surveillance; $PaO_2$:$FiO_2$, arterial partial pressure of oxygen to fraction of inspired oxygen ratio; VAP, ventilator-associated pneumonia.

| Domain | HELICS | CPIS |
|---|---|---|
| Radiological criteria | • One chest radiograph or CT showing features suggestive of pneumonia<br>• In patients with underlying cardiac or pulmonary disease, two or more serial images are required | Chest radiograph assessed and scored as:<br>• 0: No pulmonary infiltrate (0)<br>• +1: Diffuse or patchy infiltrate (+1)<br>• +2: Localised infiltrate (+2) |
| Systemic clinical features | At least one of the following:<br>• Fever (>38°C)<br>• Leukopenia or leukocytosis | Scores based on<br>• Temperature<br>• Leukocytosis or leukopenia (increased score in the presence of band form leukocytes) |
| Respiratory specific clinical features | Supportive microbiological growth **plus** one of the following **OR** two of the following without microbiological confirmation:<br>• New-onset purulent sputum<br>• Worsening gas exchange<br>• Cough, dyspnoea or tachypnoea<br>• Supportive features on auscultation | Score includes:<br>• Presence of respiratory secretions (higher score if purulent)<br>• Impaired oxygenation ($Pao_2$:$Fio_2$ <240)<br>• Culture of pathogenic bacteria (additional score for positive Gram stain) |
| Cut-off for a diagnosis of VAP | • Meets the criteria for all three domains | • A higher score indicates a higher risk of VAP. Absolute cut-offs used differ by studies |

alterations in the innate and adaptive immune system. Tracheal intubation and sedation may facilitate entry of bacteria into the lower respiratory tract by blunting mucociliary function and suppressing the cough reflex. Impaired adaptive immune response resulting from critical illness may allow microbial colonisation to progress to infection.[1] Microbial presence in the lower respiratory tract probably exists as a spectrum comprising airway colonisation, tracheobronchitis and pneumonia. The clinical consequence of the spectrum is likely to differ for each patient depending on the clinical context.[2]

## Epidemiology

VAP is an infection of the pulmonary parenchyma that occurs ≥48 h after initiation of invasive mechanical ventilation.

Amongst adults who are mechanically ventilated for ≥48 h, the global prevalence of VAP is 15–20% with an incidence of 13.6 per 1000 ventilator days.[3] Studies have reported differences in the incidence and prevalence across regions, particularly between Europe and the Americas. Observational studies in Europe report an incidence exceeding 18 per 1000 ventilator days, whereas most North American studies report an incidence between two and 16 per 1000 ventilator days.[4,5] In one observational study, Kollef and colleagues found that VAP prevalence was higher in Europe than in North or Latin America (19.4% compared with 13.5% and 13.8%, respectively).[3] However, the variation in prevalence could be attributable to differences in the criteria used to diagnose VAP, the screening methods used and the patient groups across regions.

VAP is associated with significant morbidity, mortality and increased healthcare spending. The mortality attributable to VAP is debatable, but it is estimated to be up to 13%.[6] Ventilator-associated pneumonia is associated with an increase in the duration of invasive mechanical ventilation of up to 6 days and an increase in length of stay in ICU of up to 10 days.[7] The cost of VAP to US hospital systems has been estimated to be about 40,000 USD per patient, whereas a study in the UK estimated the cost to be around £10,000 per patient.[7]

## Definitions

The 2005 joint guidelines by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) defined VAP as 'the presence of a new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin. Clinical evidence of an infectious origin includes "the new onset of fever, purulent sputum, leukocytosis and a decline in oxygenation".[8] Randomised trials with central adjudication of VAP have commonly adopted a modified version of these criteria, using a new chest radiograph infiltrate with two of leukocytosis, fever or purulent secretions to diagnose possible VAP, with definite VAP being confirmed after growth of a causative organism on a bacteriological respiratory specimen.

The US Centers for Disease Control and Prevention (CDC) recently amended reporting criteria for ventilator-associated events into ventilator-associated complications and infectious ventilator-associated complications.[9] The tool developed by the CDC is designed to screen for healthcare-associated infections using data available in electronic health records. Although sensitive, these criteria lack specificity for clinically important VAP.

Several clinical prediction scores and diagnostic criteria have been proposed to aid the diagnosis of VAP. The most commonly used tool, the Clinical Pulmonary Infection Score (CPIS), consists of a combination of criteria with different weights, comprising pyrexia, oxygenation, chest radiograph findings, leukocytosis, the character of tracheal secretion and the culture results of tracheal secretions to predict the likelihood of VAP.[10] A score >6 predicts a high probability of VAP but has poor diagnostic accuracy.[10]

The Hospitals in Europe Link for Infection Control Through Surveillance (HELICS) criteria, used for VAP surveillance across Europe, consist of clinical, radiological and microbiological criteria that classify VAP across a spectrum of five classes based on the method of sampling of the lower respiratory tract.[11] Table 1 compares and contrasts the differences between HELICS and CPIS.

Despite extensive efforts to define VAP, several limitations remain.[2] Firstly, a deterioration in oxygenation and the presence of new infiltrates on the chest radiograph are common findings in critically ill patients and are not always attributable to infection. Fluid overload, atelectasis and mucus plugging commonly complicate the course of critical illness and can be hard to differentiate from pneumonia. Secondly, the respiratory tract is not sterile; hence, microbiological samples may not always be able to delineate true infection from airway colonisation, which increases in likelihood the longer a patient remains invasively ventilated, as much as the risk of VAP.

Moreover, it is unclear how relevant the growth of an organism on respiratory tract culture is in the diagnosis of VAP. Culture of organisms may reflect respiratory tract colonisation unrelated to VAP or represent the early stage of a clinical spectrum that ends with VAP. Ventilator-associated tracheobronchitis has been suggested as an intermediatory phenomenon between airway colonisation and VAP.[2] However, it is not possible to be certain where one phenomenon ends and the next one begins. Although studies have suggested microbiological thresholds and the addition of local or systemic signs of infection to help differentiate the three phenomena (colonisation, tracheobronchitis, VAP), the suggested cut-offs and criteria have not been well validated and have not been adopted by recent guidelines.[1]

## Lower respiratory tract sampling

The lower respiratory tract can be sampled via a tracheal aspirate or a bronchoalveolar lavage using a fibreoptic bronchoscope. Both techniques have their advantages and limitations in diagnosing VAP.

Tracheal aspirates are cheap, easy to perform and minimally invasive. Tracheal aspirates allow most conventional microbiological testing, such as Gram stain microscopy and cultures, to be performed. However, given that colonisation of the proximal airway is common in patients undergoing invasive ventilation, the presence of organisms associated with VAP may not represent true infection. Culture of organisms from the trachea in patients who do not have VAP may result in the unnecessary use of antimicrobial agents increasing the prevalence of multidrug resistance in the respiratory flora. Furthermore, novel diagnostic tools such as quantitative cultures and multiplex polymerase chain reaction (PCR) tests, which are more sensitive and can produce rapid results, are not well validated using samples obtained from tracheal aspirates.

Compared with tracheal aspirates, specimens obtained using bronchoalveolar lavage in combination with quantitative culture could improve identification of patients with true VAP and optimise antimicrobial selection. However, bronchoalveolar lavage is invasive and requires more resources in terms of equipment and personnel than a tracheal aspirate. Furthermore, bronchoalveolar lavage may be poorly tolerated by patients who have severely impaired oxygenation. Non-directed bronchial lavage is less invasive than bronchoscopic sampling and involves injecting sterile saline, which is then blindly aspirated and analysed.

A meta-analysis of randomised trials reported that the use of invasive techniques compared with minimally invasive techniques among patients with suspected VAP did not improve patient-centred outcomes.[12] Current guidelines differ on the most appropriate sampling method. The 2016 IDSA and ATS joint guideline suggests the use of non-invasive sampling (including non-directed bronchial lavage) with semiquantitative cultures, whereas the 2017 European and Latin American multidisciplinary guidelines recommend the use of distal quantitative sampling to reduce antibiotic exposure in patients with suspected VAP. Both recommendations were weak and based on low-certainty evidence.[13,14]

## Novel diagnostic tools

Over recent years, new molecular methods have been developed to reduce the time from sampling to organism identification. Some assays can detect the presence of resistant genotypes, potentially alerting clinicians to the presence of multidrug-resistant organisms before microbiological sensitivities are available. A novel assay can perform a multiplex PCR test on a bronchoscopic sample, testing for up to 20 pathogens commonly responsible for VAP and up to 20 markers of resistance.[15] Studies evaluating these techniques have shown a 50–60% concordance with standard culture techniques. However, there is a risk of overdetection, as the tests cannot differentiate DNA from viable and non-viable organisms.

Another approach is testing for the presence of volatile organic compounds on heat and moisture exchanger (HME) filters. Studies have found associations between the presence of carbon disulfide and the proliferation of certain Gram-negative bacteria.[16] Heat and moisture exchanger filter analysis may detect VAP up to 3 days before clinical signs develop, potentially facilitating early detection and treatment. Currently, the technique remains a research tool with minimal translation into clinical practice.

## Risk factors

Certain patients are predisposed to developing VAP.[17] Patient-related factors include advanced age, male sex, a history of smoke exposure, immunosuppression and a history of diabetes. Specific factors related to a patient's hospitalisation also play a pivotal role in the risk of developing VAP. These include admission with a disorder of consciousness, burns or trauma, significant previous antibiotic exposure, and increased duration of invasive ventilation.

## Causative organisms

The most commonly implicated organisms are similar to those seen in other nosocomial infections and include enteric Gram-negative organisms, such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli* and *Acinetobacter* species, and Gram-positive organisms such as *Staphylococcus aureus*.[18]

There is increasing concern regarding the prevalence of multidrug-resistant organisms causing VAP. A recent meta-analysis estimated that amongst patients with *Pseudomonas* VAP, the prevalence of multidrug-resistant organisms was around 33%.[19] There were marked differences in prevalence between countries, varying between 87% and 19%. Data from

many countries were missing, which considerably reduced the precision of the estimates. Risk factors for multidrug-resistant organisms are a later onset from invasive ventilation (>5 days) and exposure to broad-spectrum antibiotics.[19]

## Strategies to prevent VAP

### Bundles of care

Since 2004, the Institution for Healthcare Improvement has advocated the use of a 'ventilator bundle', consisting of four interventions:

(i) elevation of the head of the bed to 30°;
(ii) daily trials of spontaneous awakening and breathing;
(iii) stress ulcer prophylaxis; and
(iv) venous thromboembolism prophylaxis.[20]

Multiple international societies have adopted and modified the bundle as part of guideline recommendations. Modifications include avoiding frequent ventilator circuit changes, aspiration of subglottic secretions, monitoring of the airway cuff pressure and gastric residual volume and selective decontamination of the oropharynx and digestive tract.

A recent systematic review found VAP bundles to be associated with a reduction in the incidence of VAP.[21] However, all studies were of pre- and postintervention observational cohorts, which are likely to be subject to bias. Moreover, the studies included were small, with differences between each bundle, which makes attributing effects to each intervention challenging. Based on the current evidence, our approach is to not use a bundle of care specifically targeting VAP prevention.

### Stress ulcer prophylaxis

Observational studies suggest an association between the use of proton pump inhibitors (PPIs) for stress ulcer prophylaxis and the incidence of VAP.[22] The association may be explained by an increase in gastric pH, which facilitates microbial growth in the gastrointestinal tract (GIT). The Proton Pump Inhibitors vs Histamine-2 Receptor Blockers for Ulcer Prophylaxis Therapy In Intensive Care (PEPTIC) trial was a registry-embedded multicentre trial evaluating the use of PPIs compared with histamine-2 receptor blockers.[23] The PEPTIC trial showed no difference in mortality between the two groups. However, the 95% confidence interval for the relative risk (1.00–1.10) suggests the effect is likely to range from no difference to a potential benefit with histamine-2 receptor blockers. Although associated with a significant reduction in the incidence of clinically important GIT bleeding, the use of PPIs did not reduce mortality. Rates of *Clostridioides difficile* infection were also similar between the two groups. These findings suggest that the reduction in GIT bleeding with PPIs may be offset by other adverse effects—potentially including an increased risk of VAP. Because the trial was embedded within a registry, data on VAP were not uniformly collected across all recruiting centres. However, centres in Canada that did record ventilator-associated complications found no difference between the groups.

The potential signal of harm for PPIs observed in the PEPTIC trial has not been reproduced in two large multicentre randomised trials comparing PPIs with placebo in ICU patients at risk of stress ulceration.[24,25] Both trials showed no difference in the rate of infectious complications between pantoprazole and placebo. An updated meta-analysis including these trials confirmed the findings, suggesting, with low certainty, that PPIs have no effect on the incidence of pneumonia.[26]

Current evidence suggests that the use of PPIs for stress ulcer prophylaxis is likely to be safe and not associated with an increase in VAP.

### Monitoring of gastric residual volume

Previous studies suggested an association between continuous enteral feeding and VAP.[27] Increased gastric residual volumes and associated gastro-oesophageal reflux or vomiting may lead to aspiration and the development of pneumonia. Hence, historical guidelines suggested routinely monitoring of gastric volume to guide the delivery of enteral nutrition. A multicentre randomised non-inferiority trial evaluating the effect of monitoring gastric volume on the incidence of VAP showed no monitoring to be non-inferior to routine monitoring.[28] A subsequent meta-analysis evaluating the role of frequent, less frequent and no monitoring of gastric residual volume showed no significant differences in mortality or the incidence of pneumonia between the two groups.[29] However, these findings had a low certainty of evidence. Current guidelines do not support routine monitoring of gastric residual volumes.[30] Our approach is to use gastric residual volume monitoring to guide feed tolerance rather than as a measure to prevent VAP.

### Selective decontamination of the digestive tract

Selective decontamination of the digestive tract (SDD) is a strategy for preventing infection in critically ill patients. SDD involves giving non-absorbable antimicrobial drugs to the oropharynx and digestive tract with or without a short course of i.v. antibiotics. However, routine use of SDD potentially risks promoting the emergence of multidrug-resistant organisms. The recent Selective Decontamination of the Digestive Tract in the Intensive Care Unit (SuDDICU) trial, a cluster crossover randomised trial, found no significant difference in mortality between SDD and placebo.[31] However, an updated systematic review and Bayesian meta-analysis that included the SuDDICU trial found that SDD was associated with a high probability of reducing in-hospital mortality and the risk of VAP.[32] The effect estimate was larger among studies incorporating a short course of i.v. antibiotics than those that did not.

Patients at high risk of VAP may benefit from SDD more than low-risk patients, allowing a targeted approach to its use.[33] A targeted approach could potentially reduce the risk of promoting the emergence of multidrug-resistant organisms.

Patients with reduced consciousness are a group that might benefit from SDD. They have impaired airway reflexes, which increases the risk of pulmonary aspiration of gastric contents, predisposing to VAP. Furthermore, VAP complicating an acute brain injury may exacerbate secondary brain injury through increased metabolic demand (fever) and impaired gas exchange (hypoxaemia, hypercapnia). A reanalysis of the SuDDICU trial showed patients with an acute brain injury had a significantly reduced in-hospital mortality when receiving SDD compared with standard care.[33]

Given the required engagement and agreement from local multidisciplinary services (e.g. infectious diseases, microbiology, infection prevention, pharmacy and hospital medicines

regulatory authorities), a decision to implement SDD should be contextualised to local resources and priorities.

### Prophylactic antibiotics

The role of systemic or inhaled antibiotics in preventing VAP has been investigated in several randomised trials. The Inhaled Amikacin vs Placebo to Prevent Ventilator-associated Pneumonia (AMIKINHAL) trial was a multicentre trial assessing the effect of inhaled amikacin for 3 days, commenced within 72 h of initiating invasive ventilation.[34] The primary outcome was the incidence of VAP up to day 28, adjudicated centrally by a blinded committee based on current definitions, including a positive microbiological sample from the lower respiratory tract. The investigators found a significantly reduced incidence of VAP in the inhaled amikacin arm compared with the placebo.

Two recent trials have evaluated the use of short courses of i.v. antibiotics for preventing VAP in patients with acute brain injury or impaired consciousness. François and colleagues[35] assessed the use of 48 h of amoxicillin-clavulanate compared with placebo in patients admitted to the ICU requiring invasive ventilation after an out-of-hospital cardiac arrest. Although the incidence of VAP was lower in the antibiotic group, no differences were observed in ventilator-free days or mortality. The Prevention of Early Ventilation-Associated Pneumonia in Comatose Brain Injured Patients (PROPHY-VAP) trial evaluated the effect of a single dose of ceftriaxone on the incidence of early VAP among patients with an acute brain injury (head trauma, stroke, subarachnoid haemorrhage).[36] The PROPHYVAP trial enrolled 345 patients, of which 319 were analysed for the primary outcome. The trial demonstrated a reduced incidence of early VAP (days 2–7) and an absolute reduction in mortality of 10% among those receiving antibiotics compared with placebo. A meta-analysis, which included the earlier mentioned trials, showed that, despite a significant reduction in the risk of VAP, there was no significant difference in mortality with prophylactic antibiotics compared with placebo in patients with acute brain injury undergoing invasive ventilation.[37]

The clinical trials of prophylactic antibiotics described earlier have several limitations. Firstly, VAP as an endpoint has inherent flaws, especially when the intervention involves the use of an antimicrobial agent.[2] In all three trials, VAP was centrally adjudicated based on clinical signs of infection, radiographic changes consistent with VAP and microbiological samples indicating a causative organism. Early use of antimicrobial agents may preclude laboratory growth of an organism despite the presence of VAP, biasing adjudication against VAP. Furthermore, central adjudication reduces the generalisability of the results, as captured events are not necessarily concordant with clinical diagnoses. Other potential confounding events may not be considered, such as the potential for alternative diagnoses, including atelectasis and fluid overload, which are common.

Although PROPHYVAP did show a promising mortality benefit, the effect estimate is likely to be overestimated, as the trial was not powered to detect a mortality benefit. Smaller trials with low power are more likely to report larger effect sizes than larger trials.[38]

Finally, VAP may have important consequences on the neuroprognostication of patients with brain injury because of the development of infection-related delirium. It may be difficult for clinicians to differentiate impaired consciousness caused by delirium from structural brain injury. By preventing VAP, antibiotics may reduce infection-related delirium, thereby mitigating delirium as a potential confounder during clinical neurological assessment. There is the potential for earlier withdrawal of life-sustaining therapies among patients not receiving antibiotics, leading to higher mortality compared with patients receiving antibiotics.

Although using prophylactic antibiotics to prevent VAP in patients with acute brain injuries shows promise, further trials are required to confirm any potential benefits before the strategy is adopted in clinical practice.

## Management

Figure 1 summarises the current diagnostic and treatment strategies for VAP based on the strength of evidence.

### Choice of antimicrobial drug

Current guidelines recommend that empirical treatment of VAP should be based on risk factors for multidrug-resistant organisms, the local antibiogram, clinical course and illness severity.[13] Table 2 summarises the differences between the two contemporary clinical practice guidelines for the diagnosis and management of VAP.

Patients with early-onset VAP who have no risk factors for multidrug-resistant organisms should receive a third-generation cephalosporin or a combination aminopenicillin with a β-lactamase inhibitor (e.g. amoxicillin-clavulanate).[13] However, this recommendation is weak and based on low-certainty evidence. For patients with late-onset (>5 days) VAP or risk factors for multidrug-resistant organisms, treatment should consist of a broad-spectrum antibiotic covering Gram-negative microorganisms, such as an antipseudomonal β-lactam (e.g. piperacillin-tazobactam, cefepime, meropenem). In those with a high risk of methicillin-resistant *S. aureus*, adding an antibiotic with coverage for this organism and adequate lung tissue penetration (e.g. vancomycin or linezolid) is recommended. Treatment should also be tailored to microbiological results as soon as possible to limit the development of antimicrobial resistance.

Widespread use of carbapenems such as meropenem risks increasing the prevalence of carbapenemase-producing organisms, whereas piperacillin-tazobactam may not provide adequate coverage against amp-C β-lactamase-producing organisms (e.g. *Enterobacteriacaea* species, *Serratia marcescens* and *Acinetobacter* species). For these reasons, the use of the fourth-generation cephalosporin cefepime has increased. However, recent data suggest a potential clinically important neurotoxicity with cefepime through its concentration-dependent inhibition of γ-amino butyric acid receptors. A recent trial comparing piperacillin-tazobactam with cefepime of patients requiring treatment with an antipseudomonal antibiotic showed no difference in the primary outcome of the degree of kidney injury nor the secondary outcomes of mortality or major adverse kidney events.[39] It did, however, show reduced days alive and free of delirium or coma among those treated with cefepime. We suggest that the antipseudomonal drug of choice should be guided by the local antibiogram, and if the choice between piperacillin-tazobactam and cefepime is equivocal, we recommend the

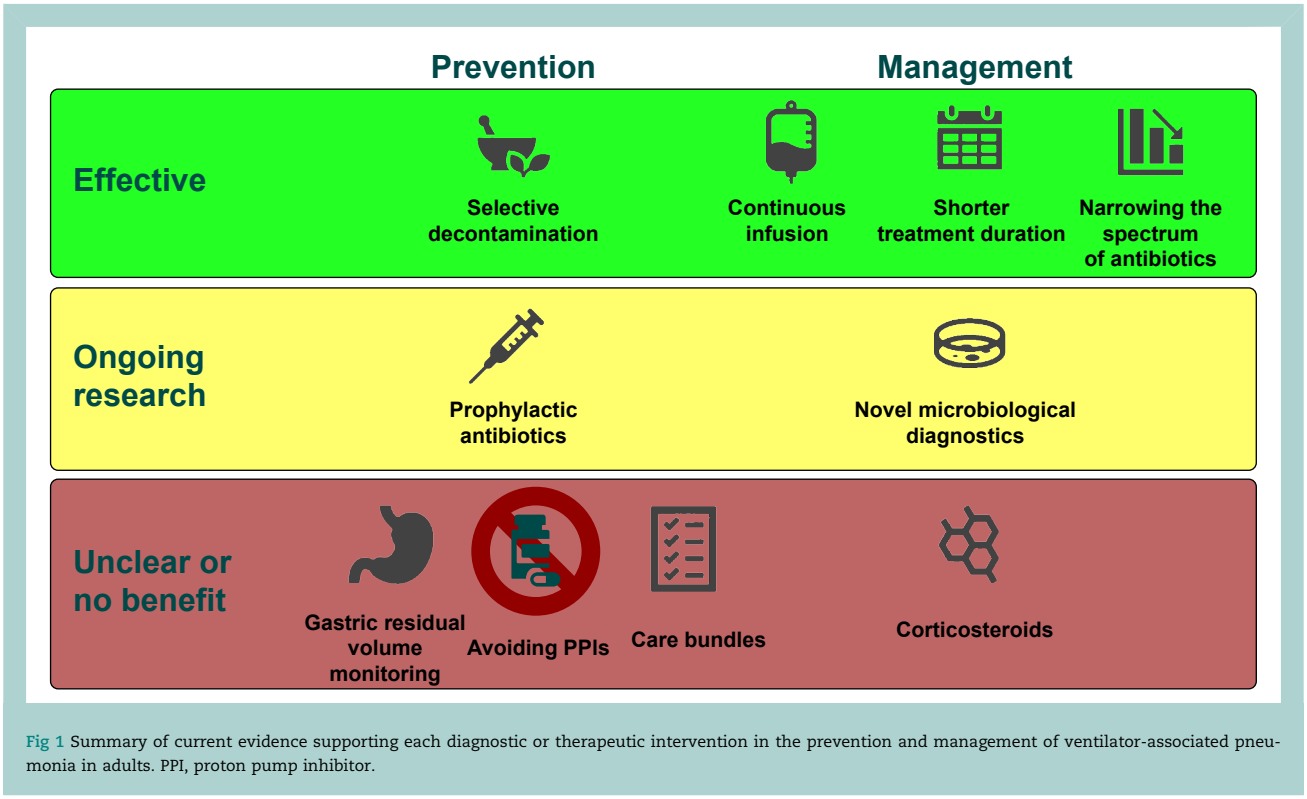


Fig 1 Summary of current evidence supporting each diagnostic or therapeutic intervention in the prevention and management of ventilator-associated pneumonia in adults. PPI, proton pump inhibitor.

use of piperacillin-tazobactam to avoid the potential for adverse neurological effects with cefepime.

## Continuous or intermittent infusions

Given that the efficacy of β-lactam antibiotics depends on the time the blood concentration is above the minimum inhibitory concentration, there is a plausible advantage of giving these agents as a continuous infusion. The recent Beta-Lactam Infusion Group III (BLING-III) trial compared a continuous infusion with an intermittent infusion of a β-lactam antibiotic (either piperacillin-tazobactam or meropenem) on mortality in critically ill patients with sepsis.[40] Among more than 7000 patients randomised, there was no difference in the unadjusted risk of mortality between the two groups, but the 95% confidence interval on the odds ratio (0.81–1.01) suggested the effect probably ranges between no difference and a clinically important effect on mortality in favour of continuous infusions. Furthermore, a prespecified adjusted analysis controlling for sex, illness severity, source of admission and type of β-lactam antibiotic used showed a significantly reduced risk of death at 90 days among patients treated with a continuous infusion compared with an intermittent infusion. A recent Bayesian meta-analysis of 18 randomised trials (which included BLING-III) showed a very high probability that prolonged infusion of β-lactam antibiotics was associated with a reduced risk of death among critically ill patients with sepsis or septic shock compared with intermittent infusion.[41] Based on the available evidence, we recommend the routine use of continuous infusions of β-lactam antibiotics for treating VAP in patients who meet criteria for sepsis or septic shock.

## Duration of treatment

Current guidelines recommend using a 7–8-day course of antibiotic therapy in patients with VAP without immunodeficiency, cystic fibrosis, empyema, lung abscess, cavitation or necrotising pneumonia, and with a good clinical response to treatment.[13] This recommendation is weak and based on moderate-certainty evidence. A meta-analysis of five trials comparing shorter (7–8 days) with longer (10–15 days) courses showed no increase in treatment failure and higher antibiotic-free days in those receiving a shorter course.[42] Even in the context of bacteraemia, there is good evidence to support a shorter duration of antibiotic therapy.[43] Patients with lung abscess, cavitation or underlying structural lung disease may require prolonged antimicrobial treatment and the duration of treatment is usually made in consultation with a specialist in infectious diseases or a microbiologist.

Treatment durations as short as 3–5 days may be appropriate for selected patients. The recent Reducing Antibiotic Treatment Duration for Ventilator-Associated Pneumonia (REGARD-VAP) trial evaluated the use of individualised shorter courses of antibiotics. The REGARD-VAP trial found that shorter courses (as short as 3–5 days) was non-inferior to longer (>7 days).[44] The investigators based their criteria for stopping antibiotics on the resolution of fever and haemodynamic instability, with a minimum duration otherwise determined by respiratory culture findings: 3 days if there was no growth on respiratory culture and 5 days if respiratory cultures grew a causative organism. If patients did not meet the criteria to stop antibiotics, they received a maximum of 7 days of treatment.

Our approach is to use a short course of antibiotics (5–7 days) in patients without significant structural lung disease who show a good clinical response to treatment.

**Table 2** Comparison of current guideline recommendations by the IDSA/ATS 2016 Clinical Practice Guideline and the Joint ERS/ESICM/ESCMID/ALAT 2017 guideline. Comments in bold-italic highlight the reasons for differences in recommendations between guidelines. CF, cystic fibrosis; ERS/ESICM/ESCMID/ALAT, European Respiratory Society, European Society of Intensive Care Medicine, European Society of Clinical Microbiology and Infectious Diseases and Latin American Thoracic Association; IDSA/ATS, Infectious Diseases Society of America and American Thoracic Society; MRSA, methicillin-resistant *Staphylococcus aureus*; VAP, ventilator-associated pneumonia.

| Domain | IDSA/ATS 2016 guidelines | ERS/ESICM/ESCMID/ALAT 2017 guidelines |
|---|---|---|
| Distal (bronchoscopy) samples with quantitative culture compared with proximal (tracheal aspirate) samples with semiquantitative culture | Proximal samples with semiquantitative culture *(Weak recommendation, low-certainty evidence)*<br><br>***The panel placed higher value on the lower risk profile, lower cost and rapid access to proximal sampling to avoid delays in antibiotic commencement*** | Distal samples with quantitative cultures *(Weak recommendation, low certainty evidence)*<br><br>***The panel placed greater importance on reducing antibiotic exposure associated with distal samples as informed by the evidence*** |
| Empirical antimicrobial therapy | Based on local antibiogram. Coverage for *Staphylococcus aureus*, *Pseudomonas aeruginosa* and other Gram-negative bacilli in all empirical regimens *(Strong recommendation, low-certainty evidence)*<br><br>***The panel placed high value on targeting the specific pathogens associated with VAP as narrowly as possible to assure adequate treatment while minimising overtreatment and its undesirable consequences by contextualising treatment to the local antibiogram*** | Antibiotics based on onset (early or late), severity and risk factors for multidrug-resistant organisms. Empirical antibiotic therapy targeting *P. aeruginosa* and extended-spectrum β-lactamase-producing organisms in patients with shock, late onset or high risk of multidrug-resistant organisms *(Strong recommendation, low certainty of evidence)*<br><br>***The panel placed high value on defining a patient group who may benefit from a narrower spectrum of antibiotic use to reduce exposure to very broad-spectrum antibiotics and reduce the risk of further antimicrobial resistance*** |
| Multiple antimicrobial empirical coverage | Anti-MRSA treatment only in those with risk factor for antimicrobial resistance *(Weak recommendation, very-low-certainty evidence)*<br><br>Two antipseudomonal antibiotics from different classes for the empirical treatment of suspected VAP only in patients with any of specific risk factors for antimicrobial resistance *(Weak recommendation, low-certainty evidence)* | Initial empirical combination therapy for high-risk VAP patients to cover Gram-negative bacteria and include antibiotic cover for MRSA in those patients at risk. A dual antipseudomonal treatment strategy should be considered for the high-risk patient who is severely ill or with septic shock *(Strong recommendation, moderate certainty of evidence)* |
| Duration of antimicrobial therapy | 7 days *(Strong recommendation, moderate-certainty evidence)* | 7–8 days in patients without immunodeficiency, CF, empyema, lung abscess, cavitation or necrotising pneumonia and with a good clinical response to therapy *(Weak recommendation, moderate certainty of evidence)* |
| Narrowing the spectrum of antibiotics | Antibiotic therapy be narrowed when susceptibility is available *(Weak recommendation, very-low-certainty evidence)* | Tailor antibiotic therapy to susceptibility and clinical response (day 3) *(Good practice statement)* |

## Supportive management

Supportive management of VAP in patients should include lung-protective ventilation, as these patients may be at risk of developing acute respiratory distress syndrome. Although systemic corticosteroids may benefit patients with severe community-acquired pneumonia, there is little evidence to support their use in the treatment of VAP.[45] Other supportive measures do not differ from other patients in ICU.

## Conclusions

Ventilator-associated pneumonia is a common complication in patients undergoing invasive mechanical ventilation in the ICU. Despite advances in prevention, few interventions have translated to a mortality benefit. Further trials focused on specific groups of patients may offer insight into a more personalised approach to prevent VAP and improve outcomes. Increasing antimicrobial resistance is likely to cause further challenges in managing VAP. However, recent advances in the

rapid and accurate diagnosis of VAP, and the optimisation of the mode and duration of therapy, may attenuate the development of multidrug-resistant organisms whilst improving outcomes.

## Declaration of interests

The authors declare that they have no conflicts of interest.

## MCQs statement

The associated MCQs (to support CME/CPD activity) are accessible at www.bjaed.org/cme/home for subscribers to *BJA Education*.

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